including insertions and **[deletions]**, are shown on an attached sheet entitled **VERSION WITH MARKINGS TO SHOW CHANGES MADE**, which follows the signature page of this amendment. As a result of this amendment, claims 1, 2, 6-10, 12, 32, 37-41, 43, 94, 94, 108, 109, 114 and 115 are pending for examination.

The following remarks address the substance of the Office Action:

Maintained Rejections

I. Matters of enablement

The Examiner has maintained the rejection to claims 38-43 under 35 U.S.C. § 112, first paragraph on the assertion that the instant specification does not teach how to produce a "derivative [which is] still immunogenic" and induces a protective immune response against *L. intracellularis* or an isolate or subspecies of *L. intracellularis* or other species of the genus *Lawsonia*.

Amended claim 38 no longer recites a derivative, and therefore, the rejection is believed to be moot. Accordingly, Applicants respectfully request withdrawal of the rejection to claims 38-43 under 35 U.S.C. § 112, first paragraph.

II. Matters of definiteness

The rejection of claims 6-9 under 35 U.S.C. § 112, second paragraph has been maintained by the Examiner on the assertion that the terms "related microorganism" in the claims is indefinite. Applicants have amended claims 6 and 7 to specify that the related microorganism "is a sub-type or isolate of *Lawsonia intracellularis*," thereby rendering the claim definite.

III. Matters of Novelty

Knittel et al.

The Examiner has maintained the rejection of claims 1, 2, 6, 7, 32, 37 and 38 under 35 U.S.C. § 102(e) over Knittel et al. (USP 5,714,375) on the assertion that Knittel's whole attenuated bacterial antigen qualifies as an 'immunogenic component' of *Lawsonia intracellularis*, inherently comprises an 'immunogenic component', or the peptide or protein of *L. intracellularis*.

The present invention is directed towards a "vaccine composition for administration to an animal, comprising: an isolated immunogenic component of *L. intracellularis* or a related microorganism, wherein said related microorganism is an isolate or sub-type of *L. intracellularis* or other species of the genus *Lawsonia*; and a pharmaceutically acceptable carrier," as recited in claim 1. Knittel et al. does not teach an isolated immunogenic component in the "antigen" of the disclosed attenuated bacteria as required by the presently claimed invention. Thus, the

rejection for anticipation fails and Applicants respectfully request withdrawal of the rejection to claims 1, 2, 6, 7, 32, 37 and 38 under 35 U.S.C. § 102(e) over Knittel.

Labigne et al.

The Examiner has maintained the rejection to claims 1, 2, 6-9 and 94 under 35 U.S.C. § 102(b) on the assertion that the claims are anticipated by Labigne et al. (WO 94/26901). Labigne, et al. disclose a recombinant immunogenic composition of *Helicobacter felis* or *H. pylori*, which may be related to *Lawsonia intracellularis*, but is not the same genus. The amended claims recite "...wherein said related microorganism is an isolate or sub-type of *L. intracellularis* or other species of the genus *Lawsonia*". Thus, Labigne does not anticipate claims 1, 2, 6-9 and 94 since there is no teaching in the cited reference of a composition comprising a member from the genus *Lawsonia*. The cited reference does not anticipate the claims and Applicants request withdrawal of the rejection to the claims under 35 U.S.C. § 102(b).

IV. The invention is non-obvious

In order for a references to render claim obvious, the reference must teach or suggest each of the elements of the claimed invention and must also provide the motivation to modify the reference to create the claimed invention. *see* M.P.E.P. 2143. As discussed below, the cited references neither suggest all of the elements of the claimed invention, nor do they provide a motivation to modify the teachings of the references to arrive at the presently claimed invention.

Joens et al.

The rejection to claims 1, 2, 6-8, 32 and 37-39 under 35 U.S.C. § 103(a) over Joens et al. (USP 5,610,059) on the assertion that Joens et al. purified PPE-causing agent make obvious the immunogenic component in the present invention.

As discussed above, the present invention is related to a vaccine comprising an "isolated immunogenic component of *L. intracellularis*..." as recited throughout the claims.

Joens et al. discloses identifying a PPE causing organism and suggest ways of producing and identifying immunogenic proteins and whole organism vaccines, methods of which were known in the art. There is no teaching or suggestion in Joens et al. for a method of vaccinating with an isolated immunogenic component from *L. intracellularis* or species of Lawsonia, nor is there any disclosure pertaining to any proteins which are specifically immunogenic. Since Joens et al. does not teach or suggest all of the claimed elements nor does it provide a motivation to modify the reference as required by M.P.E.P. 2143, it cannot render the claimed invention obvious.

In view of the above remarks, Applicants respectfully request withdrawal of the rejection to claims 1, 2, 6-8, 32 and 37-39 under 35 U.S.C. § 103(a) over Joens et al.

Labigne et al.

The rejection of claims 94 and 95 under 35 U.S.C. § 103(a) over Labigne et al. has been maintained on the assertion that the recombinant immunogenic composition of *Helicobacter felis* or *Helicobacter pylori* (a microorganism related to *Lawsonia intracellularis*) and its 67.2% relation to SEQ ID NO: 2 makes obvious polypeptide that is immunogenically cross reactive with a polypeptide comprising SEQ ID NO: 2 and comprises an amino acid sequence encoded by a nucleic acid that hybridizes to the complement of a nucleotide comprising the sequence of SEQ ID NO: 1. As discussed above, Labigne et al. does not anticipate claims 94 and 95, and fails to teach or suggest a microorganism in the *Lawsonia* genus as recited in claims 94 and 95.

Therefore Labigne et al. cannot render claims 94 and 95 obvious and Applicants respectfully request withdrawal of the rejection to claims 94 and 95 under 35 U.S.C. § 103(a).

New Rejections

I. Under 35 U.S.C. § 112, first paragraph

Description of "derivative"

The Examiner has rejected claims 9 and 38-40 and claims 1, 32 and 41 under 35 U.S.C. § 112, first paragraph on the assertion that the claims contain subject matter which was not described in the specification, specifically "wherein the derivative is still immunogenic" in claims 9 and 38-40 and "wherein said related microorganism is...subspecies of *L. intracellularis*" in claims 1, 32 and 41.

Amended claims 9, 38 and 40 no longer recite the terms "derivative" and "wherein the derivative is still immunogenic," thereby rendering the rejection to the claims moot. Amended claims 1, 32 and 41 recite the phrase "...wherein said related microorganism is...sub-type of *L. intracellularis*." As stated above, this finds support in the filed specification on page 3, lines 27-29.

Matters of enablement

Claims 1, 2, 6-10, 12, 32, 37-41, 43, 94, 95, 108, 109, 114 and 115 have been rejected under 35 U.S.C. § 112, first paragraph on the assertion that the isolated immunogenic component of the claimed invention has not been shown to be effective in inducing a 'protective' immune response against homologous infection by a *L. intracellularis* isolate or against a heterologous infection by a subspecies of *L. intracellularis* or any other species of the *Lawsonia* genus.

Contrary to the Examiner's assertion, the Applicants have shown that compositions according to the claimed invention are protective against infection. Example 11 teaches a formalin-killed *L. intracellularis* vaccine composition and Example 12 gives a vaccination protocol of three groups: infected controls, vaccinated and uninfected controls. The pigs who survived the vaccination protocol were challenged with the vaccine (Example 13). Example 14 provides for antibodies from vaccinated pigs which recognize various immunodominant proteins. The pathology (Example 16) of the three groups and histopathology (Example 17) describe intestinal disorders in the infected control group and no gross signs of PPE (Example 16) or conclusive evidence of PIA (Example 17) in the vaccinated group. Thus, Applicants have described and enabled a vaccination and challenge in the exemplified formalin-killed *L. intracellularis* vaccine composition.

Moreover, as described in the specification, specific parts of *L. intracellularis* have been demonstrated to be immunogenic, and the proteins that elicit the strongest antibody action have been identified. SEQ ID NOs have been provided of polynucleotides and polypeptides which function in this capacity, for example SEQ ID NO: 2 (polypeptide) and 7-8, 10, 11, 13, 14, 16-20 and 22-27 (*see* page 11, lines 18-21). Methods of detecting immunogenic components have been described in the specification on page 16, lines 1-8 in reference to US Patents. The Examples describe arriving at the immunogenic components, *see* for example, Examples 4, 5 and 9.

The Examiner is asserting that experimental proof that specific components work as a vaccine is required in order to enable the presently claimed invention. However, specific immunogenic parts of *L. intracellularis* have been enabled and proteins which elicit antibody reactions have been enabled in the present disclosure. A composition for a vaccine as well as a method of utilizing this vaccine has been enabled by the present disclosure. Thus, the present invention has been enabled by the disclosure since elements of the present invention have been taught by the disclosure.

In addition, the Examiner has rejected claims 41, 43 and 109 under 35 U.S.C. § 112, first paragraph on the assertion that the specification is non-enabling for a polypeptide that is 40% similar to SEQ ID NO: 2 and induces a 'protective' immune response against an isolate of *L. intracellularis* or related *Lawsonia* microorganism.

The Examiner asserts that without a disclosure of the specific amino acid residues contained within the claimed peptide that one of ordinary skill in the art cannot be sure of the sequence embraced by the claims, or be able to use such a sequence without undue experimentation. The Applicants submit that they have provided the sequence disclosure in SEQ ID NO: 2 as well as its intended function in a vaccine composition of the invention. In

addition, further guidance as to the desired homology has been provided in the specification. In view of the subject area, and subject matter, one of skill in the art is enabled for a polypeptide that is 40% similar to SEQ ID NO: 2 in the composition of the invention. The polypeptide is to be used to elicit an immune response in order to deter an intestinal disease condition in an animal. Thus, the provided claimed polypeptide, the availability of homology analysis by the varied computer programs in the art utilizing extensive databases, such as BLAST and one of skill in the art would be enabled to identify and utilize a polypeptide according to the claimed invention for its incorporation into a vaccine composition to be used in a method according the invention. The specification provides for a vaccine composition as described above to aid intestinal disease in an animal, including the essential components. One of skill in the art would be not have to undergo undue experimentation with regards to utilizing a polypeptide according to SEQ ID NO: 2 since the specification provides the necessary guidance to identify a candidate homologous sequence. The Examples provide for various molecular tools in order to obtain an immunogenic component according to the invention which one of skill in the art could use.

In view of the above, Applicants respectfully request withdrawal of the rejection to the claims under 35 U.S.C. § 112, first paragraph

II. Matters of definiteness

Claims 1, 2, 6-9, 32, 37-41, 43, 94, 95, 114 and 115 are rejected under 35 U.S.C. § 112, second paragraph on the assertion that the claims recite phrases which render the claim(s) indefinite.

claims 1, 32 and 41

Claims 1, 32 and 41 have been rejected for the recitation of the phrase "...subspecies of *L. intracellularis* or other species of the genus *Lawsonia*..." In addition, the Examiner is rejecting the claims on the assertion that "...immunogenic component of *L. intracellularis* or related microorganism, wherein said related microorganism is an isolate...of...*L. intracellularis*" requires clarification. Applicants submit that amended claims 1, 32 and 41 now include "...sub-type of *L. intracellularis*..." which is a well understood term to one in the art. Further, one of skill in the art is aware of the natural variants of microorganisms that exist within a genus and species which acquire such names as "strains," "sub-type" and/or "isolates" within the art. Finally, Applicants submit that one of skill in the art would not find the phrase "other species of the genus *Lawsonia*" unclear. This encompasses non-*intracellularis* species of the *Lawsonia* genus that exhibit characteristics similar to that of sp. *intracellularis*.

Scope of claim 6

Claim 6 has been rejected on the assertion that the phrase "related microorganism" broadens the scope of claim 6 (dependent upon claim 1). Amended claim 6 defines the limitation of "related microorganism" and further limits claim 1, rendering it definite.

"...immunogenic component is...SEQ ID NOS:..."

Claim 114 has been rejected on the assertion that the recitation of "immunogenic component is...SEQ ID NOS:..." is vague and indefinite and that it is unclear whether these SEQ ID NOS: represent a polynucleotide or polypeptide. Amended claim 114 clarifies that the SEQ ID NOS: represent a polypeptide.

claims 94 and 95

Claim 95 has been rejected on the assertion that the recitation of "immunologically" is indefinite and confusing in terms of effective amounts of a polypeptide. Amended claim 95 contains the phrase "an immunogenically effective amount" which is both clear and definite to one in the art (*see* page 4, line 20). Claims 94 and 95 have been rejected on the assertion that it is unclear how a polypeptide can be immunologically cross reactive with another polypeptide. Amended claims 94 and 95 do not contain the phrase "...polypeptide that is immunologically cross reactive with a polypeptide." And the recitation of "...related microorganism..." within claim 95 has been deemed vague and indefinite. Applicants submit amended claim 95 clarifies what "related organism" is intended to encompass, thus rendering the rejection inapplicable. Amended claims 94 and 95 address the Examiner's concerns.

"...comprises...polypeptide..."

The Examiner has rejected claim 43 on the assertion that the claim depends from claim 38 which does not provide antecedent basis for "the immunogenic component comprises...polypeptide." Applicants respectfully submit that claim 43 is dependent from claim 41, which provides/provided the antecedent basis for the phrase in question.

"...a refolding and heat shock protein..."

Claims 9 and 40 are rejected on the assertion that the phrase "a refolding and heat shock protein..." is confusing. Amended claims 9 and 40 address the Examiner's concerns by reciting a protein, "wherein said protein is a refolding protein, a heatshock protein, or the combination thereof." (*see* page 6, lines 6-10).

In view of the above remarks, Applicants respectfully request withdrawal of the rejection to the claims under 35 U.S.C. § 112, second paragraph.

Objections to the claims

The Examiner has objected to claims 114 and 115 for including non-elected subject matter. Applicants submit that amended claim 114 and pending claim 115 are directed towards elected subject matter since they merely recite that the claimed vaccine may also include the proteins (claim 114) or the precursor of the encoded protein. Amended claims 1, 6, 7, 32, 41, and 95 now recite a preceding article before the recitation of "related microorganism."

Conclusion

Claims 1, 6-9, 12, 32, 37-40, 43, 94, 95, 108 and 114 have been amended to correct minor informalities and define the present invention. Support for these amendments is found in the filed specification as discussed above. Should any issues remain that may be addressed by a phone conversation, the Examiner is invited to contact the undersigned at the phone number listed below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LPL

Dated: 2 December 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. **(Amended three times)** A vaccine composition for administration to an animal, comprising:

an isolated immunogenic component of *L. intracellularis* or a related microorganism, wherein said related microorganism is an isolate or **[subspecies]**sub-type of *L. intracellularis* or other species of the genus *Lawsonia*; and

a pharmaceutically acceptable carrier.

6. **(Twice amended)** The vaccine composition according to Claim 1, wherein said immunogenic component comprises at least one macromolecule selected from the group consisting of a peptide, a protein, a carbohydrate, a lipid and a nucleic acid from *L. intracellularis* or a related microorganism, said macromolecule being present in an amount effective to induce a protective immune response against *L. intracellularis* or a related microorganism, wherein said related microorganism is a sub-type or isolate of *Lawsonia intracellularis*.

7. **(Amended three times)** A vaccine composition according to Claim 6, further comprising a further peptide or protein from *L. intracellularis* or a related microorganism, wherein said related microorganism is a sub-type or isolate of *Lawsonia intracellularis*.

8. **(Twice amended)** The vaccine composition according to claim 7, wherein the **[polypeptide]**protein is a recombinant **[polypeptide]**protein from *L. intracellularis* or a sub-type or isolate of *Lawsonia intracellularis*.

9. **(Amended three times)** The vaccine composition according to Claim 7, further comprising a compound selected from the group consisting of: a **[refolding and heatshock]** protein, wherein said protein is a refolding protein, a heatshock protein, or the combination thereof, a flagellar basal body rod protein, an S-adenosylmethionine:tRNA ribosyltransferase-isomerase, an autolysin, an enoyl-(acyl-carrier-protein) reductase, and a glucarate transporter**[, and a derivative of any of the above, wherein said derivative is still immunogenic]**.

12. **(Amended four times)** The vaccine composition of claim 10, wherein the polypeptide is encoded by a nucleic acid comprising SEQ ID NO:1.

32. **(Amended)** A method for vaccinating an animal against infection by *L. intracellularis* or a related microorganism**[, wherein said related microorganism is an isolate or subspecies of *L. intracellularis* or other species of the genus *Lawsonia*]** or treating an animal infected by *L. intracellularis*, said method comprising the step of:

administering to said animal an effective amount of an isolated immunogenic component of *L. intracellularis* or a related microorganism, wherein said related microorganism

is an isolate or **[subspecies]**sub-type of *L. intracellularis* or other species of the genus *Lawsonia* for a time and under conditions sufficient to induce a protective immune response against *L. intracellularis* or said related microorganism.

37. **(Twice amended)** A method according to Claim 32, wherein said isolated immunogenic component comprises at least one of a peptide, protein, carbohydrate, lipid or nucleic acid molecule or a combination thereof from *L. intracellularis* or the related microorganism in an amount effective to induce a protective immune response against *L. intracellularis* or said related microorganism.

38. **(Twice amended)** The method according to Claim 37, wherein said isolated immunogenic component comprises a peptide**[,]**or protein**[or a derivative thereof]** from *L. intracellularis***[, wherein said derivative is still immunogenic]**.

39. **(Twice amended)** The method according to claim 38, wherein the peptide or protein is in recombinant form.

40. **(Twice amended)** **[A]**The method according to Claim 32, wherein the isolated immunogenic component is selected from the group consisting of: a **[refolding and heatshock]** protein, wherein said protein is a refolding protein, a heatshock protein, or the combination thereof, a flagellar basal body rod protein, an S-adenosylmethionine, tRNA ribosyltransferase-isomerase, an autolysin, an enoyl-(acyl-carrier-protein) reductase, and a glucarate transporter**[, and a derivative of any of the proteins, wherein said derivative is still immunogenic]**.

43. **(Twice amended)** The method of claim 41, wherein the polypeptide is encoded by a nucleic acid comprising SEQ ID NO:1.

94. **(Amended three times)** A vaccine composition for administration to an animal comprising an immunogenically effective amount of a polypeptide **[that is immunologically cross reactive with a polypeptide]** comprising the sequence of SEQ ID NO: 2 and comprises an amino acid sequence encoded by a nucleic acid that hybridizes to the complement of a nucleotide comprising the sequence of SEQ ID NO: 1 under hybridization conditions comprising at least about 16% (v/v) formamide to at least about 30% (v/v) formamide and at least about 0.5M salt to at least about 0.9M salt at a temperature of 42°C, wherein said related microorganism is an isolate or sub-type of *L. intracellularis* or other species of the genus *Lawsonia*.

95. **(Amended three times)** A method of vaccinating an animal against infection by *L. intracellularis* or a related microorganism or treating an animal infected by *L. intracellularis* said method comprising the step of: administering to said animal an **[immunologically]**immunogenically effective amount of a polypeptide **[that is immunologically cross reactive with a polypeptide]** comprising the sequence of SEQ ID

NO:2 or an amino acid sequence encoded by a nucleic acid that hybridizes to the complement of SEQ ID NO: 1 under hybridization conditions comprising at least about 16% (v/v) formamide to at least about 30% (v/v) formamide and at least about 0.5M salt to at least about 0.9M salt at a temperature of 42°C, wherein said related microorganism is an isolate or sub-type of *L. intracellularis* or other species of the genus *Lawsonia*.

108. **(Amended)** The vaccine composition of claim 10, wherein the animal is a pig.

114. **(Amended)** The vaccine composition of Claim 1, wherein said isolated immunogenic component **[is]**further comprises a polypeptide selected from the group consisting of: SEQ ID NOS: 2, 4, 7, 9, 10, 12, 14, and 16.